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EXAMINER: ALLEN, M

18M1/0823

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1812	5

DATE MAILED: 08/23/93

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

preliminary amendments information disclosure statement 3/22/93

☒ This application has been examined ☒ Responsive to communication filed on 5/17/93 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), 0 days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☑ Notice of References Cited by Examiner, PTO-892.
2. ☑ Notice re Patent Drawing, PTO-948.
3. ☑ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, Form PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☑ Claims 1, 11-12, 15-31, 58-73 are pending in the application.

   Of the above, claims _____ are withdrawn from consideration.

2. ☑ Claims 2-10, 13-14, 32-57 have been cancelled.

3. ☐ Claims _____ are allowed.

4. ☑ Claims 1, 11-12, 15-31, 58-73 are rejected.

5. ☐ Claims _____ are objected to.

6. ☐ Claims _____ are subject to restriction or election requirement.

7. ☑ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.

8. ☐ Formal drawings are required in response to this Office action.

9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable. ☐ not acceptable (see explanation or Notice re Patent Drawing, PTO-948).

10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____ has (have) been ☐ approved by the examiner. ☐ disapproved by the examiner (see explanation).

11. ☐ The proposed drawing correction, filed on _____, has been ☐ approved. ☐ disapproved (see explanation).

12. ☐ Acknowledgment is made of the claim for priority under U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.

13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.

14. ☐ Other

EXAMINER'S ACTION

Claims 2-10, 13-14, and 32-57 have been canceled. Claims 60-73 have been added by preliminary amendment. Claims 1, 11-12, 15-31 and 58-73 are under consideration by the Examiner.

This application filed under 37 C.F.R. § 1.60 lacks the necessary reference to all of the prior applications. A complete statement reading "This is a Continuation of application Serial No. 824,740, filed 1/21/92, which is a Continuation of application Serial No. 480,691, filed 2/15/90, now abandoned, which is a Continuation-in-part of application Serial No. 196,909, now abandoned" should be entered following the title of the invention or as the first sentence of the specification. Also, the present status of all parent applications should be included.

It is noted that the preliminary amendment filed 22 March 1993 references only the 824,740 application. It is further noted that the oath refers to the 480,691 and 196,909 applications. It is presumed that applicant intends to claim benefit to all of the parent applications.

Claims 1, 11-12, 19-31, and 58-73 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-7, 9-27, 33, 35, and 37 of copending application Serial No. 07/894,213. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant human t-PA glycosylation variants, compositions, and methods of treatment encompass the claimed embodiments of the co-pending application.

This is a <u>provisional</u> obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

The obviousness-type double patenting rejection is a judicially established doctrine based upon public policy and is primarily intended to prevent prolongation of the patent term by prohibiting claims in a second patent not patentably distinct from claims in a first patent. <u>In re Vogel</u>, 164 USPQ 619 (CCPA 1970). A timely filed terminal disclaimer in compliance with 37 C.F.R. § 1.321(b) would overcome an actual or provisional rejection on this ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 C.F.R. § 1.78(d).

Applicant is requested to bring to the attention of the Examiner any other co-pending applications containing similar

subject matter.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order

for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

Claims 1, 11, and 58-59 are rejected under 35 U.S.C. § 103 as being unpatentable over Goeddel et al. (U.S. Patent No. 4,766,075).

Goeddel et al. discloses human t-PA, pharmaceutical compositions containing it, and methods of treatment. This t-PA is produced recombinantly in E. coli and CHO cells using vectors. Yeast and other suitable host cells are taught for its production. Goeddel et al. suggest making amino acid modifications or mutations to human t-PA which do not alter the biological activity of human t-PA. (See column 5, lines 21-58.) Goeddel et al. does not suggest particular positions to mutate.

Claim 1 encompasses and claim 11 claims t-PA variants which include N64S66 t-PA, N64T66 t-PA, and N250 t-PA. These modifications provide an Asn-X-Ser or Asn-X-Thr tripeptidyl sequence or glycosylation site.

It would have been obvious to modify the DNA sequence encoding human t-PA at any amino acid position as suggested by Goeddel et al. to produce variant human t-PA with the same biological activity using appropriate vectors and host cells as taught by Goeddel et al. One would have been motivated to do so in order to produce active t-PA proteins which would have benefit in thrombolytic therapy.

While DNA sequences encoding the named tripeptidyl sequence may result in glycosylation at the Asn when the DNA sequence is

transcribed and translated not every tripeptidyl sequence encoded actually results in glycosylation.

It is noted that there is no evidence of record that the variants N64S66 t-PA, N64T66 t-PA, and N250 t-PA have an altered biological activity. The proteins having these substitutions and those others for which no data is present are deemed to be obvious over Goeddel et al. Likewise, the compositions and methods of treatment are deemed to be obvious.

Claims 1, 11-12, 15-31, 58-59, 61, 63, 66, 68, 70, and 72 are rejected under 35 U.S.C. § 112, first paragraph, as the disclosure is enabling only for claims limited as outlined below. See M.P.E.P. §§ 706.03(n) and 706.03(z).

The specification supports some modifications t-PA, u-PA and prourokinase. It does not support <u>any</u> modifications to streptokinase or other molecules that may be capable of converting plasminogen to plasmin which applicants have included in their definition of "plasminogen activator."

The claims encompass addition of O-linked and N-linked glycosylation. The specification does not describe the O-linked glycosylation patterns of native plasminogen activators such that one of ordinary skill in the art would know which plasminogen activator variants are "not glycosylated in the corresponding native plasminogen activator." The amino acid residues where O-linked glycosylation naturally occurs in the various plasminogen

activators is not detailed. Furthermore, the specification fails to teach how to make an O-linked glycosylation linkage at a selected hydroxyamino acid where it would not normally occur. The recitation of chemical or enzymatic coupling of glycosides to proteins is not deemed to be enabling as the essential information cannot be incorporated by reference. No other information is provided in the specification in reference to O-linked glycosylation of plasminogen activators.

Claim 1 recites a plasminogen activator variant that exhibits fibrinolytic activity and is glycosylated at one or more regions that are not glycosylated at one or more regions that are not glycosylated in the corresponding native plasminogen activator. The specification provides particular embodiments of such variants which do not support the vast spectrum of modified plasminogen activators encompassed by this claim. No guidance on selecting other sites or combinations of sites is provided. It would constitute undue experimentation to determine other variants having novel glycosylation sites which would have the claimed fibrinolytic property.

The specification only describes and enables modifications to human t-PA. No other species of t-PA or other plasminogen activators (e.g. urokinase or streptokinase) are described or enabled.

With respect to claim 15 which depends upon claim 1, it is not clear from the specification which plasminogen activators

other than t-PA have a finger domain. It appears from the originally filed claims that this claim is intended to be limited to t-PA.

Claim 11 recites a tissue plasminogen activator variant that has novel N-linked glycosylation sites at particular sites within its growth factor domain. However, no guidance is provided on selecting combinations of the named sites as claimed in part (11). It would constitute undue experimentation to determine which variants having other combinations of novel N-linked glycosylation sites in the growth factor domain would have the claimed fibrinolytic property.

Claim 18 is directed to a variant further comprising additional modifications in the (1) 205-215 region, (2) 244 to 255 region, (3) 233-242 region, or (4) two or more of (1),(2), and (3). The specification provides no guidance on selecting the combinations of positions to be modified, what these modifications should be, or how they are to be made. It would constitute undue experimentation to determine which other variants having novel glycosylation sites would have the claimed fibrinolytic property.

With respect to claims 19-23 which depends upon claim 1, it is not clear from the specification which plasminogen activators other than t-PA are susceptible to enzymatic cleavage or may occur in multiple chain forms. For example, urokinase does not have a cleavage site at amino acid position 275. (See claims 23-

28.) It appears from the originally filed claims that this claim is intended to be limited to t-PA.

Claims 19-23 are directed to variants resistant to enzymatic cleavage. However, applicants provide no data testing the activity of such a modified t-PA. This information is essential and cannot be incorporated by reference. The unpredictability involved in obtaining mutated t-PA's with particular characteristics and activities requires further description and enablement. Insufficient guidance is provided for selecting mutations to render resistance to enzymatic cleavage. It would constitute undue experimentation to determine which other variants would have the claimed resistance to enzymatic cleavage and fibrinolytic properties.

Claim 29 is directed to a variant in which an alteration is introduced into the protease domain of t-PA. Claim 30 recites particular positions or ranges of positions to be modified. As the protease domain extends from about amino acid 264 through the C-terminal end of the molecule at amino acid 527, such alterations at any or all positions are not supported by the specification. No guidance on selecting sites or combinations of sites is provided. It would constitute undue experimentation to determine which protease domain alterations would have the claimed properties. Furthermore, it is unclear what is meant by the terms "alteration" and "zymogenic activity." While examples of "alterations" are provided, the meets and bounds of this term

are not. There is no description or definition in the specification that would enable one to know what is meant by the term "zymogenic character." The description and details of making these variants are essential and cannot be incorporated by reference.

With respect to modification of amino acid positions 296-299 in claims 30, 61, and 66, no combinations of amino acids other than substituting alanine at each of positions 296-299 are set forth in the specification as being suitable.

It would constitute undue experimentation to determine all other combinations of substitutions at amino acid positions 296-299 that would result in a fibrinolytically active human t-PA variant.

It is noted that applicant incorporates by reference application Serial No. 384,608, now U.S. Patent 5,108,901, for further description and enablement of these 296-299 mutants. (See specification pages 21-22.) This material is deemed to be essential matter to these claims. However, this patent does not appear to enable any substitutions of amino acid positions 296-299 other than each position being substituted by alanine either.

The disclosure is objected to because of the following informalities: the specification at page 20, line 19, discloses that known glycosylation sites of human t-PA exist at amino acid

positions 117, 184, 210, and 448. The specification at page 4, line 24, discloses that the known potential glycosylation sites of human t-PA exist at amino acid positions 117, 184, 218, and 448. The recitation of amino acid position 210 on page 20, line 19, is a clear typographical error and should be corrected. One of ordinary skill in the art would recognize that this is not the correct amino acid position. As a result of this error, claims 63-64 and 68-69 lack antecedent basis in the specification. The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 C.F.R. § 1.75(d)(1) and M.P.E.P. § 608.01(l).

In addition, claim 73 is objected to for containing a typographical error, "cindition."

Correction is required.

The following reference is cited as being of interest.

Gething et al. (U.S. Patent No. 5,041,376) discloses proteins having supernumerary N-linked oligosaccharide side chains which shield functional sites or epitopes and genes encoding them.

Papers related to this application may be submitted to Group 180 by facsimile transmission. Papers should be faxed to Group 180 via the PTO Fax Center located in Crystal Mall 1 (CM1). The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 308-4227.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marianne

P. Allen whose telephone number is (703) 308-0666.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

GARNETTE D. DRAPER
PRIMARY EXAMINER
ART UNIT 1812